UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,074	08/28/2003	Michael James Paul Arthur	117-473	7212

23117 7590 03/22/2006

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,074	ARTHUR ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,15,16 and 23-29* is/are pending in the application.

4a) Of the above claim(s) *9-10, 12-14, 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,15,16 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/05 &7/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction of invention

Applicant's election with traverse of restriction requirement in the reply filed on Jan13, 2006 is acknowledged. Applicant elects with traverse the invention Group VII for further prosecution on merits. Applicant traverses on the grounds that no undue burden would be placed on the examiner for searching all of claims 1-27. This is not found persuasive for reasons of record in the restriction requirement mailed on 10/13/2005. The requirement is still deemed proper and is therefore made FINAL.

Claims **1-8, 11, 15, 16, and 23-29** are pending and presently under examination with respect to elected invention.

Specification

Priority date for the elected invention, applied under 35 USC §119 (e) for the provisional Application is granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims **1-8, 11, 15, 16, and 23-29** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

The above claims are directed to a method of treating liver disease by specific induction of hepatic stellate-cell apoptosis wherein wherein said apoptosis inducer is sulfasalizine or a derivative thereof.

The scope of the instant claims encompass a method of treating any and all liver diseases in any and all subjects comprising administering for selective delivery to hepatic stellate cells by undisclosed routes (any and all routes) an undisclosed amount of any and all inducers of hepatic stellate cell apotosis. Further, said inducer of apoptosis needs an undisclosed stellate cell specific receptor on the cell surface for targeting the drug to and for specific triggering of stellate cell apoptosis. Further claims encompass sulfasalazine and any and all derivatives thereof that are capable of inducing hepatic cell apoptosis and introducing to said subject an undisclosed implant in an undisclosed location and containing said inducer/s, treat liver cirrhosis, treat fibrosis caused by several agents including pathogens, consumed alcohol, exposure to chemicals, drugs, etc, or due to inherited condition. Further claims include kits containing undisclosed inducer/s of HSC apoptosis with know how of administering the inducer or selectively administering the inducer.

With respect to the elected invention instant specification however only provides guidance and/or evidences regarding assessment of sulfasalizine on hepatic stellate cells grown in vitro where a dose dependent increase in apoptosis and caspase 3 activity was observed (Example 4). And results indicating that an in vivo treatment with sulfasalizine of the hepato-toxin carbon tetrachloride injected adult rats resulted in livers with less accumulation of collagen or fibrosis when compared to sulfasalizine untreated control rat livers by 72 hrs has been presented (example 5).

The specification however, does not present representative number of enabled evidences for broad claims treating of all liver diseases in all subjects (organisms), does not present enabled evidences to support the following: specific apoptosis of the hepatic stellate cells of livers treated in vivo with sulfasalizine, selective delivery of sulfasalizine to hepatic stellate cells, delivery vehicles for sulfasalizine (e.g. liposome), treatment of liver cirrhosis, treatment fibrosis caused by pathogens or consumed alcohol or exposure to chemicals or any drugs or any inherited conditions etc., the claimed stellate cell receptors specific to sulfasalizine or its delivery vehicle, the use of claimed implants or liver implants for treating with sulfasalizine. Further specification does not provide specific description of the kits of the elected invention.

Given the relative paucity or absence of evidences in the art regarding claimed methods of using sulfasalizine or its derivatives in the treatment of a liver disease it is incumbent upon the applicant to provide enabled descriptions of the claimed methods and sufficient number of examples to support the full scope and breadth of the claims. In the absence of adequate description commensurate with the scope and the breadth of the claims one of ordinary skill in the art would conclude that the inventor(s), at the time the application was filed, was not in possession of the broadly claimed invention. Claiming all divergent species that achieve a result as contemplated by the application without defining the means and/or uses will do so not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

With respect to elected invention instant specification is enabled, at the best, for sulfasalizine induced apoptosis of hepatic stellate cells in culture and

sulfasalizine induced reduction of activated stellate cells and collagen accumulation in liver of a rat induced to develop carbon-tetrachloride induced fibrosis.

Claims 1-8, 11, 15, 16, and 23-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sulfasalizine induced apoptosis of hepatic stellate cells in culture and sulfasalizine induced reduction of activated stellate cells and collagen accumulation in liver of a rat induced to develop carbon-tetrachloride induced fibrosis, does not provide enablement for the full scope, which embraces selective delivery to hepatic stellate cells, vehicles for hepatic stellate cell specific sulfasalizine delivery, liver implants for the delivery of sulfasalizine, treatment of all liver diseases including cirrhosis and fibroses or kits with know how for selective administration of sulfasalizine to hepatic stellate cells in vivo. It does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate with the full scope of the claims as explained below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope and breadth of the instant claims, read in the light of instant specification and the state of the art at the time of filing encompass treatment of all liver

diseases using any and all agents and their derivatives that are inducers of hepatic cell specific apoptosis, sulfasalizine delivery in to HSCs and use of a liver implant. In absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the species completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability. Examiner, having read the instant specification broadly in the light of the Art, finds that such is not the case and hence concludes that the instant application does not reasonably provide enablement for the full breadth and scope of the claims and would have required undue experimentation for a skilled artisan to make and **use** the full scope of the methods as claimed.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

***Guidance of the Specification and the Existence of Working Examples*:** With respect to the elected invention instant specification however only provides guidance and/or evidences regarding assessment of sulfasalizine on hepatic stellate cells grown in vitro where a dose dependent increase in apoptosis and caspase 3 activity was observed. Further results of an in vivo treatment with sulfasalizine of a rat with a carbon tetrachloride liver firbrosis accumulates less of collagen than untreated control rats has been presented. The specification however, does not present representative number of enabled evidences for claimed treatment of all liver diseases in any subjects or a method of selective delivery of sulfasalizine to hepatic stellate cells or delivery vehicles for the same or the treatment of liver cirrhosis or fibrosis caused by pathogens, alcohol consumption, drugs, inherited conditions etc. or stellate cell receptors specific for

sulfasalizine or its delivery vehicle or liver implants for specific delivery of sulfasalizine. Given the state of the art coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods as claimed.

State of the Art, the Predictability of the Art: Art is still unpredictable with regard to therapeutic interventions for liver fibrosis as indicated by Bataller et al (2005, The Journal of Clinical Investigation 115:209-218) et al., states "Although many therapeutic interventions are effective in experimental models of liver fibrosis, their efficacy and safety in humans is unknown" (p.209. abstracts) and "A limitation of the current antifibrotic approaches is that antifibrotic drugs are not efficiently taken up by activated HSCs and may produce unwanted side effects. Cell specific delivery to HSCs could provide a solution to these problems" (p.216, col.1, 2nd paragraph). Bataller concludes "developing simple and reliable noninvasive markers of hepatic fibrosis is an important goal in clinical hepataology and will facilitate the design of clinical trials" (p.216, col.2, 2nd paragraph). With regard to sulfasalizine there still exists apprehension regarding its side effects as evident in the literature Watkinson et al (1986, Drugs 32:1-11) indicates that include for example neurotoxiciy, hepatotoxicity, pulmonary fibrosis, skin rashes etc and hence a number of less toxic alternatives to sulfasalazine have been devised and undergoing trial (abstract). Marinos et al (1992, J. Clin. Gastroenterol 14:132-135) indicates severity in two cases of massive hepatic necrosis associated with sulfasalazine quote "these two cases remind us one of the potential hazards of sulfasalazine at a time when alternative therapies are now available"(abstract). Thus the unpredictability in the art, at the time of instant filing, regarding the site specific delivery of drugs for hepatic fibrosis as well as regarding side effects of sulfasalizine one of ordinary skill in the art finds the claimed invention as highly unpredictable and undue experimentation to practice the invention in its fully claimed scope.

Amount of experimentation necessary: The invention as claimed is not enabled because one of skilled in the art would not be able to rely upon the state of the art to successfully predict a priori an agent that induces apoptosis and further will not be

able to predict that any of it gives rise to are inducers of apoptosis, one skilled in the art would not be able to predict claimed hepatic cell specific delivery of sulfasalazine into hepatic stellate cells through cell surface receptors as no art exists as of effective filing date. Accordingly, in view of the lack of teachings in the art and lack of guidance provided by the specification with regard to representative number of claimed agents of hepatic cell specific apoptosis inducers or their derivatives and in view of lack of an enabled use of a method of treatment of a liver disease or conditions by stellate cell specific delivery of sulfasalazine as of filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of sulfasalazine induced apoptosis of hepatic stellate cells in culture and sulfasalazine induced reduction of activated stellate cells and collagen accumulation in liver of a rat induced to develop carbon-tetrachloride induced fibrosis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-8, 11, 15, 16, and 23-29** are rejected under 35 USC 103 (a) as being unpatentable over Lang et al., (1999, Ital. J. Gastroenterol. Hepatol. 31:173-179) and further in view of Liptay et al.,(1999, British Journal of Pharmacology 128:1361-1369).

The above claims are directed to a method of treating liver disease by specific induction of hepatic stellate-cell apoptosis wherein wherein said apoptosis inducer is sulfasalizine or a derivative thereof.

Regarding claims 1-8 Lang teaches role of hepatic stellate cell (HSC) apoptosis in hepatic cell fibrosis and a method of preventing or clearing hepatic ell fibrosis by

stellate cell apoptosis (p.173, abstract). Further Lang teaches with art reference that apoptosis may be the main mechanism behind the disappearance of the HSCs during resolution of hepatic fibrosis. He further teaches a molecular mechanism that may mainly be responsible for hepatic stellate cell apoptosis wherein active transcription factor nuclear-factor kappaB (NFκB) pathway generally acts to protect cells from apoptosis by inducing the transcription of multiple antiapoptic proteins that inhibit apoptosis. Cells in which NFkB is lacking or inhibited lead to enhanced suceptability to apoptosis (p.176 col.2, 2nd paragraph bridging p.177, col.1). However Lang does not teach sulfasalizine as an inhibitor NFκB transcription pathway.

Liptay teaches that sulfasalizine, an anti-inflammatory drug, mediates strong inhibition of NF-κB activity and potent induction of apoptosis (p.1361, col.1, abstract). In conclusion Liptay further teaches that sulfasalizine induced apoptosis may explain why treatment with it leads to claearance of inflammatory cells and therefore can break the cycle of unrelenting cellular activation and tissue damage in chronic inflammation (p.1368, col.2 3rd paragraph).

Thus it would have been obvious for one of ordinary skill in the art to incorporate into method of treating hepatic fibrosis by activating apoptosis of hepatic stellate cells using an inhibitor of NFκB transcription pathway. One of ordinary skill in the art would have reasonable expectation of success using the methods of inhibiting hepatic stellate cell apoptosis using sulfasalizine as apoptosis inducer to treat hepatic fibrosis of a subject because of the teachings of Lang and Liptay as above.

Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through

Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanna

Patent Examiner

Art Unit 1633

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER
3/20/06